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APPLICATION NO.	FILING DATE	FIRST NAMED INVENTOR	ATTORNEY DOCKET NO.	CONFIRMATION NO.
09/393,803	09/10/1999	MARGARET A. LIU	19188PCA	3309

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EXAMINER
LEFFERS JR, GERALD G

ART UNIT	PAPER NUMBER
1636	

DATE MAILED: 05/20/2003

19

Please find below and/or attached an Office communication concerning this application or proceeding.

Office Action Summary	Application No.	Applicant(s)	
	09/393,803	LIU ET AL.	
	Examiner	Art Unit	
	Gerald G Leffers Jr.	1636	

-- The MAILING DATE of this communication appears on the cover sheet with the correspondence address --

Period for Reply

A SHORTENED STATUTORY PERIOD FOR REPLY IS SET TO EXPIRE 3 MONTH(S) FROM THE MAILING DATE OF THIS COMMUNICATION.

- Extensions of time may be available under the provisions of 37 CFR 1.136(a). In no event, however, may a reply be timely filed after SIX (6) MONTHS from the mailing date of this communication.
- If the period for reply specified above is less than thirty (30) days, a reply within the statutory minimum of thirty (30) days will be considered timely.
- If NO period for reply is specified above, the maximum statutory period will apply and will expire SIX (6) MONTHS from the mailing date of this communication.
- Failure to reply within the set or extended period for reply will, by statute, cause the application to become ABANDONED (35 U.S.C. § 133).
- Any reply received by the Office later than three months after the mailing date of this communication, even if timely filed, may reduce any earned patent term adjustment. See 37 CFR 1.704(b).

Status

1)☒ Responsive to communication(s) filed on *03 March 2003* .

2a)☐ This action is **FINAL**. 2b)☒ This action is non-final.

3)☐ Since this application is in condition for allowance except for formal matters, prosecution as to the merits is closed in accordance with the practice under *Ex parte Quayle*, 1935 C.D. 11, 453 O.G. 213.

Disposition of Claims

4)☒ Claim(s) *50-77* is/are pending in the application.

4a) Of the above claim(s) _____ is/are withdrawn from consideration.

5)☒ Claim(s) *50-68,70-73 and 75-77* is/are allowed.

6)☒ Claim(s) *69 and 74* is/are rejected.

7)☐ Claim(s) _____ is/are objected to.

8)☐ Claim(s) _____ are subject to restriction and/or election requirement.

Application Papers

9)☐ The specification is objected to by the Examiner.

10)☒ The drawing(s) filed on *03 March 2003* is/are: a)☒ accepted or b)☐ objected to by the Examiner.

Applicant may not request that any objection to the drawing(s) be held in abeyance. See 37 CFR 1.85(a).

11)☐ The proposed drawing correction filed on _____ is: a)☐ approved b)☐ disapproved by the Examiner.

If approved, corrected drawings are required in reply to this Office action.

12)☐ The oath or declaration is objected to by the Examiner.

Priority under 35 U.S.C. §§ 119 and 120

13)☐ Acknowledgment is made of a claim for foreign priority under 35 U.S.C. § 119(a)-(d) or (f).

a)☐ All b)☐ Some * c)☐ None of:

1.☐ Certified copies of the priority documents have been received.

2.☐ Certified copies of the priority documents have been received in Application No. _____ .

3.☐ Copies of the certified copies of the priority documents have been received in this National Stage application from the International Bureau (PCT Rule 17.2(a)).

* See the attached detailed Office action for a list of the certified copies not received.

14)☐ Acknowledgment is made of a claim for domestic priority under 35 U.S.C. § 119(e) (to a provisional application).

a) ☐ The translation of the foreign language provisional application has been received.

15)☐ Acknowledgment is made of a claim for domestic priority under 35 U.S.C. §§ 120 and/or 121.

Attachment(s)

1) ☐ Notice of References Cited (PTO-892)
2) ☐ Notice of Draftsperson's Patent Drawing Review (PTO-948)
3) ☐ Information Disclosure Statement(s) (PTO-1449) Paper No(s) _____ .
4) ☐ Interview Summary (PTO-413) Paper No(s). _____ .
5) ☐ Notice of Informal Patent Application (PTO-152)
6) ☐ Other: .

DETAILED ACTION

Receipt is acknowledged of an amendment, filed 3/3/03 as Paper No. 18, in which applicants cancelled the pending claims and resubmitted the claims as claims 50-77. This was done at the examiner's request in order to simplify examination and eventual publication of any allowed claims.

Because new rejections are made herein, this action is not final. Rejection of claim 69 on grounds of lack of enablement are made here upon further consideration of the application as a whole. If applicants have questions concerning the basis for this rejection, they are encouraged to contact the examiner at the number listed below. Additional rejections under 112 2nd paragraph are made in order to clean up the claims prior to allowance and were not necessitated by applicants' amendment of the claims.

Drawings

The corrected drawings submitted on 3/3/03 have been reviewed by the Draftsperson and are acceptable.

Claim Rejections - 35 USC § 112

The following is a quotation of the first paragraph of 35 U.S.C. 112:

> The specification shall contain a written description of the invention, and of the manner and process of making and using it, in such full, clear, concise, and exact terms as to enable any person skilled in the art to which it pertains, or with which it is most nearly connected, to make and use the same and shall set forth the best mode contemplated by the inventor of carrying out his invention.

Claim 69 is rejected under 35 U.S.C. 112, first paragraph, as containing subject matter which was not described in the specification in such a way as to enable one skilled in the art to

which it pertains, or with which it is most nearly connected, to make and/or use the invention.

This is a new rejection.

Enablement is considered in view of the Wands factors (MPEP 2164.01(A)). These include: nature of the invention, breadth of the claims, guidance of the specification, the existence of working examples, state of the art, predictability of the art and the amount of experimentation necessary. All of the Wands factors have been considered with regard to the instant claims, with the most relevant factors discussed below.

Nature of the invention: Claim 69 is directed towards a method of co-expressing in a single cell *in vivo* at least two gene products from a vector comprising multiple cistrons, at least one of which comprises a sequence encoding an immunogenic epitope from HIV. The only disclosed use for the claimed method is for producing a therapeutic or protective immune response in an animal, including humans, against HIV infection. The nucleic acids of the inventions comprise up to several cistrons per nucleic acid construct which cistrons are either under the control of individual promoter/regulatory elements or feature two or more cistrons operatively linked to a first promoter/regulatory element (e.g. via an IRES sequence located between different cistrons such that a single transcript produces multiple polypeptides upon translation in the cell). The invention thus encompasses the complex expression of multiple coding sequences from single nucleic construct in eukaryotic cells. Moreover, the invention encompasses the use of coordinated expression of gene products and interaction between expressed gene products and the nucleic acid construct itself to affect the ultimate expression of the desired antigenic HIV polypeptide *in vivo* (e.g. expression of rev from the same construct comprising a rev-dependent gene). Finally, the invention encompasses the additional expression

of immuno-stimulatory gene products from the same construct in order to enhance the level and type of immune response against the desired polypeptide. Thus, the claimed invention is exceedingly complex on multiple levels from transgene expression in eukaryotic cells to coordinate expression of gene products to stimulation of the immune response of a vertebrate organism via the expression of "foreign" genes in vivo.

Breadth of the claims: Given the broadest reasonable interpretation of the rejected claim upon reading the specification, the claim reads upon the vaccination of a vertebrate animal, specifically humans, against infection by HIV. Thus, the breadth of the rejected claims, encompassing a vaccine against a pathogen for which no effective vaccine is known even at this time, only exacerbates the extreme complexity of the claimed invention.

Guidance of the specification: The specification provides many permutations of different nucleic acid constructs bearing multiple cistrons that can be tried in an effort to develop a safe and effective HIV vaccine. Guidance is given for different types of constructs wherein the different cistrons are each transcribed under the control of separate regulatory elements or wherein the different cistrons on a given construct are transcribed as part of a single, polycistronic message. Different combinations of immunostimulatory and antigenic coding sequences are described which might be tried in order to develop an effective immune response against a pathogenic organism from which the antigen coding sequence is derived. There is no significant guidance, however, with regard to making the construction and use of such an anti-HIV vaccine in humans more predictable than had already been demonstrated in the art at the time of applicants' filing of the instant application.

The existence of working examples: Although applicants test various polynucleotide constructions in mice and primates, these systems are not acknowledged models that would reflect the human conditions (e.g. see Haynes below). The specification provides examples wherein nucleic acid constructs of the invention were used to generate an anti-gp120 response in mice, anti-gp160 response in primates (i.e. the rhesus monkey and African green monkey) and an anti-SIV response in primates. The anti-gp120 response in mice demonstrated that the polycistronic vectors described as part of the instant invention are more effective than the equivalent combination of monocistronic vectors in generating a specific immune response against gp120. However, as noted above, none of the model systems described by applicants is accepted in the art as being predictive of success for developing such an anti-HIV vaccine or protective response in humans. Moreover, applicants own examples demonstrate that the generation of a sustained, specific immune response in lower primates is not necessarily predictable with the nucleic acid constructs of the instant invention. In the case of an anti-SIV response, applicants' construct generated a specific CTL response against SIV gag that is subdued over time. No such specific CTL response was obtained for equivalent constructs expressing SIV nef (e.g. Example 4).

State of the art: The art of vaccinating vertebrate organisms against viral infections, at the time of filing of the instant application, was well developed. However, the unique challenges presented by the HIV virus, due to its nature of attacking the helper T cell subset, present heretofore insurmountable challenges. "The difficult scientific issues before us underlie the fact that, as yet, there is no preventive HIV vaccine on the near horizon with clear prospects for clinical use." (Haynes, page 1279, column 1). "Although more is known about HIV than almost

any other infectious agent, scientific questions remain unanswered that are critical to development of an HIV preventative vaccine." (Haynes, page 1279, column 3). Further, there are no animal models for human infection. "Because of a lack of an animal model of human AIDS and because a cohort of individuals naturally resistant to HIV infection is not available, the immune correlates of protection against HIV are not known." (page 1280, column 1). Thus, the state of the art with regard to an immune response by humans against HIV, remains underdeveloped and extensive experimentation of a discovery nature is ongoing.

Predictability of the art: The art of vaccinating a vertebrate host organism against HIV viral infection or viral epitopes is unpredictable. At the time of applicants' invention, there was no model organism that exhibited an immune response to HIV that was correlative with that of humans. It is also known in the art that the surface antigens of the virus mutate rapidly, thus evading immune responses and that no protective immunity has been raised against HIV, even to date. Thus, the art of vaccinating a vertebrate against HIV infection is unpredictable.

The amount of experimentation necessary: Given the extreme complexity of the invention, featuring the use of nucleic acids directly injected into the tissue of an organism that must coordinately express multiple genes *in vivo* and that must generate an immune response against at least one of the gene products; given the fact that the breadth of the claims encompasses a vaccine against a pathogen for which no such effective vaccine has been developed; given the lack of significant guidance in the specification on how to make and use such nucleic acid constructs to generate such an *in vivo* immune response against HIV; given the lack of relevant working examples and the fact applicants' own examples with primates are not predictable (much less predictable of success in humans); given the state of the art at the time of

the invention where no such vaccine against HIV was known nor was thought to be available any time in the near future; and given the resulting unpredictability of the art that arises from the fact that no such vaccine has been developed to date, and the fact that HIV attacks the very cell population responsible for specific anti-viral response and the nature of the highly mutable HIV virion, one of skill in the art would not be able to construct and use the claimed invention without undue, unpredictable experimentation. Thus, applicants' invention of polycistronic nucleic acid constructs and methods for inducing a protective immune response against HIV in vertebrate animals, including humans, is not considered enabled by the instant specification.

The following is a quotation of the second paragraph of 35 U.S.C. 112:

> The specification shall conclude with one or more claims particularly pointing out and distinctly claiming the subject matter which the applicant regards as his invention.

Claim 74 is rejected under 35 U.S.C. 112, second paragraph, as being indefinite for failing to particularly point out and distinctly claim the subject matter which applicant regards as the invention.

Claim 74 is vague and indefinite on several grounds.

- Part 9 recites the limitation of "using" a gene from a clinical isolate. It would be remedial to amend the claim to delete the words "using a gene" and insert therefore the term "obtained".
- Part 12 recites the limitation of "several mutations on several constructs such as variable loop removal". The use of "such as" renders the claim indefinite in that it is unclear whether the mutation necessarily comprises a variable loop deletion.

- Part 15 is vague and indefinite in that the metes and bounds of the phrase "rev: for gp160 and gag dicistronics" are unclear. The phrase "for gp160 and gag dicistronics" appears to be intended use language which does not carry any weight. Alternatively, the phrase could be taken to mean that rev is only used when two of the cistrons of the nucleic acid encode gp160 and gag. If this is intended, then the limitation is confusing as several rev sequences are included in the Markush group of claim 74.
- Parts 15-19 all recite a nucleic acid sequence when the claim states "wherein each of the first, second, and optionally third cistrons encode a combination of any two to three of the following". It appears that parts 15-19 are intended to specify the cistron encodes a particular protein and not a particular nucleotide sequence.
- Parts 18-19 specify that the nucleotide sequence encodes multiple proteins, when the specification makes clear that each cistron encodes a single protein sequence. It appears the limitation may be intended to recite that the cistron encodes a interleukin or tumor associated antigen.

Conclusion

Claims 50-68, 70-73 and 75-77 are allowed. Claims 69 and 74 are rejected.

Any inquiry concerning this communication or earlier communications from the examiner should be directed to Gerald G Leffers Jr. whose telephone number is (703) 308-6232. The examiner can normally be reached on 9:30am-6:00pm.

If attempts to reach the examiner by telephone are unsuccessful, the examiner's supervisor, Remy Yucel can be reached on (703) 305-1998. The fax phone numbers for the organization where this application or proceeding is assigned are (703) 305-7939 for regular communications and (703) 305-7939 for After Final communications.

Any inquiry of a general nature or relating to the status of this application or proceeding should be directed to the receptionist whose telephone number is (703) 308-0196.

Gerald G Leffers Jr.
Examiner
Art Unit 1636

Ggl
May 19, 2003